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Review

The role of inflammatory cytokines and NF-κB/MAPK signaling pathways in the evolution of familial Mediterranean fever: Current clinical perspectives and potential therapeutic approaches

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ABSTRACT

Familial Mediterranean fever (FMF) is one of the social and health care problems for several populations that is known as a historically endemic disease of inflammatory nature. FMF, albeit a rare disorder, is characterized by recurrent fevers and painful inflammation of various body parts, especially the abdomen, lungs, and joints. FMF is typically characterized by inflammation of the abdominal lining (peritonitis), inflammation of the lining surrounding the lungs (pleurisy), painful, swollen joints (arthralgia and occasionally arthritis), and a characteristic ankle rash, a condition that is referred to as recurrent polyserositis, or familial paroxysmal polyserositis. Moreover, FMF is an inherited inflammatory disorder usually occurring in people of Mediterranean origin – including Sephardic Jews, Arabs, Armenians, and Turks; but it may ostensibly affect any other ethnic group, however, rarely. While there’s no cure for this disorder, FMF is typically diagnosed during childhood, and signs and symptoms are treatable – or even preventable – by specialized medical attrition. The inflammatory signaling pathways associated with the evolution of FMF are currently being unraveled has that has therapeutic repercussions. In this review, I recap major concepts associated with the cellular and molecular immunology of FMF, especially shedding light on the likely roles of inflammatory cytokines, the transcription factor nuclear factor (NF)-κB, and the superfamily of mitogen-activated protein kinases (MAPKs). Furthermore, I summarize current advances for the clinical treatments available for FMF.

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1. Epidemiology and episodes of FMF

Familial Mediterranean fever (FMF) is an inherited recessive condition (Fig. 1), essentially characterized by recurrent episodes of painful inflammation, particularly in the abdomen, chest, or joints [1]. These episodes are often accompanied by fever, and sometimes a rash [2].

The early episodes usually occur in childhood or teenage years, but in some cases, the initial attack occurs much later in life. Typically, episodes last from 12 to 72 h, and can vary in the degree of severity [2]. The length of time between attacks is also variable and, sometimes, unpredictable. Without treatment to help prevent attacks and complications, a buildup of certain inflammatory protein deposits (commonly referred to as amyloidosis) in the body’s organs and tissues may occur, which can lead to negative inflammatory responses [2], retroperitoneal fibrosis [3], and possible kidney failure [4].

Epidemiologically, FMF primarily affects populations originating in the Mediterranean region, particularly people of Armenian, Arabic, Turkish, and Jewish ancestry [5]. Etiologic scanning reveals that the disorder affects from 1 in 250 people to 1 in 1000 people in these populations of Mediterranean descent [6,7]. It is less common, however, in other populations or ethnic groups [7,8]. For general characteristics of FMF, refer to Table 1.

2. The cellular and molecular immunology of FMF

Genetically speaking, it is now established that mutations in the MEFV (Mediterranean fever) gene can predispose to, or even cause, FMF [9–12]. The MEFV gene (cytotegenic location: 16p13.3) (Fig. 2), which belongs to a superfamily of genes called TRIM (trypartite motif-containing) [10], provides instructions for coding a systemic protein called pyrin (comprising of 781-amino acid), also known as marenostrin, and particularly found in white blood cells (WBCs) [11]. This protein is closely involved in the immune system, specifically with the regulation of the process, and propagation of, the inflammatory response [2].
2.1. Pyrin protein and the MEFV gene

Pyrin is produced in certain WBCs – neutrophils, eosinophils, and monocytes – that are known to play a particular role in inflammation, and in combating impending infection [11]. For example, it has been reported that pyrin may direct the migration of WBCs (chemotaxis) to sites of inflammation, and regulate or even down-regulate the exaggerated inflammatory response [2,13].

At the molecular level, pyrin has been reported to interact with other molecules of the cellular milieu involved in the process of infection and the inflammatory response [2]. Research evidence indicates that pyrin may help regulate inflammation particularly by interacting with the cytoskeleton, by modifying the structural framework of the cell [2,14].

Furthermore, mutations in the MEFV gene have been shown to reduce the activity of the pyrin protein, thus disrupting control of the inflammatory process [1,2,9]. An inappropriate or prolonged inflammatory response can therefore result in pain in the specified areas of the abdomen, chest, or joints, a situation usually accompanied by fever, as indicated above [2,4].

On the identification of mutations associated with FMF, to date more than 80 MEFV-related mutations that may cause FMF have been identified [1,9]. Few mutations have been reported to cause the deletion of short segments of DNA from the MEFV gene, which can lead to an abnormally small, albeit dysfunctional, protein [9]. Most MEFV mutations, however, may alter one of the protein building blocks used to make pyrin, hence the inflammatory consequences [2]. Therefore, screening for the set of the most common mutations and detection of a single mutation appear to be sufficient for delineating the presence of specific clinical symptoms concurrently identified for the diagnosis of FMF [1,2,9].

The most common mutation replaces the amino acid methionine (Met) with valine (Val) at protein position 694 (Met694Val or M694V) [9,15]. Among people with FMF, this particular mutation is also associated with an increased risk of developing amyloidosis, a complication in which abnormal protein deposits can lead to kidney failure [4,16].

In addition to the aforementioned, recent evidence suggests that variations in another gene, known as SAA1 (see below), can further modify the risk of developing amyloidosis among people with the M694V mutation [2].

Other, non-predominant MEFV mutations, however, have been reported [2]. These mutations include A744S, E148Q, F479L, M680I, M694I, P369S, R761H, and V726A. With the exception of E148Q, all MEFV mutations are located in the portion of exon 10 in most populations [17,18].

2.2. The SAA1 gene and FMF

Normal variations in another gene, the SAA1 (serum amyloid A1), may also modify the course of FMF (Fig. 3) [19]. There is evidence to suggest that a particular version of the SAA1 gene (called the α variant) may increase the risk of amyloidosis among people with FMF [2].

The SAA1 gene encodes serum amyloid A1; this protein is made primarily in the liver, and circulates in low levels in the blood. Although its function is not fully understood, serum amyloid A1 appears to play a critical role in regulating the immune system [20].

Furthermore, it has been reported that serum amyloid A1 may help repair damaged tissues, act as an antibacterial agent, and signal the migration of germ-fighting cells to sites of infection [21]. Levels of serum amyloid A1 have been reported to increase in blood and other tissues under conditions of inflammation [2,15].

There are three known versions of the SAA1 protein, known as α, β, and γ, which, biochemically, differ by one or two amino acids [19]. The frequency of these variants differs across populations. In Caucasian populations, for example, the α version predominates, while the γ version is rare. In the Japanese population, however, the three versions appear almost roughly equally [22].
version of the SAA gene that encodes SAA2 is involved with FMF but to a lesser extent than SAA1 [23].

Several studies indicated that having the α version of the SAA1 protein increases the risk of amyloidosis [2,19], which involves the buildup of protein deposits that can lead to kidney failure if left untreated [4]. Moreover, studies provide evidence that individuals with FMF who also have the α version of the protein are two- to seven-fold more likely to develop amyloidosis than are people with either the β or γ version [19].

It is established that more SAA1 is produced during episodes of inflammation such as those that occur with FMF [12]. This protein and other related compounds may form abnormal clumps in organs and tissues by deposition. It remains unclear, however, how the α version of SAA1 increases the susceptibility to contracting amyloidosis (or alternatively, how the β and γ versions may protect against this complication) in individuals with this disorder. However, accumulating evidence indicates that SAA1 may interact with a transcription factor, known as SAA activating factor (SAF), which has been implicated in the sustained expression of amyloidogenic SAA under chronic inflammatory conditions [24].

2.3. Molecular testing of FMF

Molecular testing is usually carried out to screen the MEFV mutations for diagnosis of patients with a clinical suspicion of FMF. For this purpose, genomic DNA is typically isolated from peripheral blood using special kits, and subsequently analyzed [1,2].

The aforementioned kits usually provide materials for the isolation of DNA from human whole blood, the in vitro amplification of MEFV gene sequences, and the subsequent detection of several mutations by reverse-hybridization [1].

In short, the FMF test is based on the reverse-hybridization principle, and includes three successive steps: (i) DNA is isolated from anticoagulated blood by a rapid and convenient procedure. Then, (ii) MEFV gene sequences are simultaneously in vitro amplified, and biotin-labeled in a single ('multiplex') amplification reaction. Finally, (iii) the amplification products are selectively hybridized to a test strip, which contains oligonucleotide probes (wild type- and mutant-specific) immobilized as parallel lines. Bound biotinylated sequences are detected using streptavidin–alkaline phosphatase and color substrates (chromogenic development) [1,2].

3. An overview of the genetics of FMF

As previously indicated, FMF is almost always inherited in an autosomal recessive pattern – the so-called conventional inheritance – which means both copies of the gene per cell should have the mutation [1]. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene (carriers), but they typically do not show signs and symptoms of the condition (see Fig. 1). This is usually the typical inheritance of FMF [2,25].

In rare cases, however, the FMF condition appears to be inherited in an autosomal dominant pattern, in which one copy of the altered gene in each cell is sufficient to cause the disorder, and affected individuals often inherit the mutation from one affected parent [26]. Nevertheless, there are other possible explanations of this unusual pattern. A gene mutation that occurs frequently in a population may result in a disorder with autosomal recessive inheritance appearing in multiple generations in a family, a pattern that mimics autosomal dominant inheritance [2]. If one parent has FMF (with two mutations in the MEFV gene) and the other parent is an unaffected carrier, it may appear as if the affected child inherited the disorder only from the affected parent. This appearance of autosomal dominant inheritance when the pattern is actually autosomal recessive is called pseudo-dominance [1,2,26].

4. The clinical manifestations and diagnosis of FMF

4.1. Diagnostic criteria and clinical observations

As indicated, FMF is a hereditary autosomal recessive, auto-inflammatory disorder characterized by recurrent, self-limiting episodes of short duration of fever and serositis [1,2]. FMF is the most frequent periodic febrile syndrome among the auto-inflammatory syndromes, a heterogeneous group of recently identified diseases, clinically characterized by recurrent febrile attacks, in the absence of auto-antibodies and antigen-specific T lymphocytes. While not an infectious disease, FMF is exacerbated with the onset of inflammation such as those that occur with FMF [31]; (ii) elevated erythrocyte sedimentation rate (ESR), which is also an indication of an inflammatory response [29,30]; (iii) elevated plasma fibrinogen, a cofactor for blood clotting [30]; (iv) elevated serum haptoglobin, an index of red blood cell destruction, a common occurrence in rheumatic diseases, such as FMF [31]; (v) elevated C-reactive protein (CRP), typical of acute episodes of inflammation [31]; and (vi) elevated albumin in the urine, demonstrated by urinalysis; the presence of albumin in urine can technically be a symptom of kidney disease, along with microscopic hematuria (very small – microscopic – amounts of blood or blood cells in the urine), during attacks [5]. Features for the typical diagnosis of FMF are given in Table 2.

4.2. Therapeutic approaches to FMF

There is no known cure for FMF. The treatment for FMF is essentially treatment of symptoms. Attacks in FMF are known to be are self-limiting, and thus require analgesia and non-steroidal anti-
inflammatory drugs (such as diclofenac) [1]. Since the 1970s, colchicine, a drug otherwise mainly used in gout that reduces inflammation, has been shown to decrease attack frequency in FMF patients. The exact way in which colchicine suppresses attacks is unclear, however. While colchicine is not without side-effects (such as abdominal pain and muscle pains), it may markedly improve quality of life in patients; the dosage is typically 1–2 mg a day. Moreover, development of amyloidosis is delayed with colchicine treatment. Although colchicine intoxication remains severe, long-term daily colchicine is a relatively safe and effective drug. Currently, interferon is being studied as a therapeutic modality [1,2]. Furthermore, recent advances are aiming at developing new drugs that interfere with the pyrin ring for molecular intervention, and blocking the cytokines/FMF interface by targeting NF-κB/MAPK signaling pathways (see below).

5. The molecular pathways associated with FMF

Despite the enormous amount of information relating to the pathogenesis of FMF, little is known about the cellular and molecular pathways involved with this disorder. Recent data indicate that this and related illnesses represent inborn errors in the regulation of innate immunity [11]. Pyrin, the protein mutated in FMF (see above), defines an N-terminal domain found in a large family of proteins involved in inflammation and apoptosis [2]. Through this domain pyrin may play a role in the regulation of cytokines, such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α, transcription factors such as nuclear factor (NF)-κB, kinases such as mitogen-activated protein kinase (MAPK), and leukocyte apoptosis [1,2].

5.1. NF-κB–FMF interface

NF-κB is a dimeric transcription factor that is involved in the regulation of a large number of genes that control various aspects of immunity and inflammatory responses [32–36]. This transcription factor is activated by a variety of stimuli ranging from cytokines, to various forms of radiation, to oxidative stress. Recent studies have advanced our understanding of the signal transduction pathways leading to NF-κB activation by cytokines that will provide insights for the mechanism by which NF-κB is regulated in FMF [2].

A crucial question that is yet to be answered is whether FMF plays a physiological role in NF-κB activation. An important and widely investigated transcription factor, therefore, that is a major participant in signaling pathways governing cellular responses to inflammatory reactivity, characteristic of FMF, is NF-κB [4,37]. First identified as a factor that regulates the expression of the immunoglobulin κ light chains in B lymphocytes, NF-κB is also recognized as a sequence-specific transcription factor involved in the activation of an exceptionally large number of genes in response to inflammation, viral and bacterial infections, and other stressful situations requiring rapid reprogramming of gene expression such as in oxidative challenge [32–36].

In unstimulated cells under resting conditions (inactive state), NF-κB exists as homo- or heterodimers of members of the Rel family. The dimers of NF-κB are sequestered in the cytosol through non-covalent interactions with inhibitory proteins, termed IκBs. The translocation and activation of NF-κB in response to various stimuli, such as cytokines (IL-1 and TNF-α), microbial agents (lipopolysaccharide-endotoxin; LPS), oxidative challenge (ROS/RNS), and irradiation (UV and γ-rays), are sequentially organized at the molecular level [32–36].

In brevity, NF-κB activation occurs through the signal-induced phosphorylation of a multi-subunit upstream kinase, termed IκB kinase (IKK), by NF-κB inducing kinase (NIK). Stimulation leads to rapid phosphorylation of IκB, thereby marking it for ubiquitylation, and ultimately proteolytic degradation. This exposes the nuclear localization signal (NLS) on NF-κB, thus allowing the nuclear translocation of the subunits and activation of the transcription of target genes [32–36].

IκB-independent pathways, however, have been recently recognized as alternative factors that regulate the activation of NF-κB. As an example, direct phosphorylation of RelA (p65), the major transactivating member of the IκB family, has been shown to regulate NF-κB activation in one of two of its transactivation domains [32]. A further mechanism was revealed for NF-κB regulation with the discovery of transcription factor-IB-Ι/D (TF-IB/D) and TATA-binding protein (TBP), recognized as two important regulators of NF-κB transcriptional activity. The dominant-negative form of the mitogen-activated protein kinase (MAPK) expression vector abrogated the interaction of TF-ΙΙD/TBP with a co-transfected His-p65 fusion protein, and selective inhibition of MAPK [38] by SB-203580 reduced TF-ΙΙD/TBP in vitro [32,34]. Finally, modulating the intracellular redox equilibrium constitutes a potential mechanism that can manipulate and dictate the localization and activation of NF-κB [32–36]. The role of this transcription factor in FMF would certainly shed light on the molecular pathways involved with the mutations closely associated with this disorder.

Recent studies have shown that pyrin regulates caspase-1 activation and IL-1β production through the interaction of its N-terminal PYD (pyrin domain) motif with the ASC (apoptosis-associated speck-like protein) adapter protein, and also modulates IL-1β production by interaction of its C-terminal B30.2 domain with the catalytic domains of caspase-1 [2,37]. This mechanism has been shown to be NF-κB dependent, particularly involving the p65 subunit [38]. Furthermore, it has been reported that high levels of TNFR1 at the cell surface in patients with certain FMF mutations may hypersensitize cells to stimulation by TNF, thus leading to increased NF-κB p65 subunit activation, and an exaggerated proinflammatory response [39].

Furthermore, it has been shown that a TNF receptor splice mutation (TNFRSF1A) was associated with increased NF-κB activation in patients with tumor necrosis factor receptor-associated periodic syndrome (TRAPS), characteristic in FMF [40]. This indicated that cytokine receptors may be involved with the mechanism
associated with the NF-κB reactivity during acute inflammatory responses. The aforementioned is corroborated by observations involving TNF-mediated activation of the MEFV promoter in a NF-κB-dependent manner [41,42].

5.2. MAPK–FMF interface

Mitogen-activated protein (MAP) kinases were identified by virtue of their activation in response to growth factor stimulation of cells in culture, hence the name mitogen-activated protein kinases (MAPK) [43-50]. MAPKs have similar biochemical properties, immuno-cross-reactivity, amino acid sequence, and ability to in vitro phosphorylate similar substrates. Maximal MAPK activity requires that both tyrosine and threonine residues are phosphorylated [45]. This indicates that MAPKs act as switch kinases that transmit information of increased intracellular tyrosine phosphorylation to that of serine/threonine phosphorylation.

Although MAPK activation was first observed in response to activation of epidermal growth factor (EGF), platelet-derived growth factor (PDGF), nerve growth factor (NGF) and insulin and insulin-like receptors, other cellular stimuli such as T cell activation (which signals through the Lck tyrosine kinase), phorbol esters (that function through activation of protein kinase C (PKC)), thrombin, bombesin and bradykinin (that function through G-proteins), as well as N-methyl-D-aspartate (NMDA) receptor activation and electrical stimulation rapidly induce tyrosine phosphorylation of MAPKs [43–50].

MAPKs are, however, not the direct substrates for receptor tyrosine kinases (RTKs) or receptor-associated tyrosine kinases but are in fact activated by an additional class of kinases termed MAP kinase kinases (MAPKK kinases) and MAP kinase kinases (MAPKKK kinases). One of the MAPKs has been identified as the proto-oncogenic serine/threonine kinase, Raf. Ultimate targets of the MAPKs are several transcriptional regulators such as serum response factor (SRF) and the proto-oncogenes Fos, Myc, and Jun, as well as members of the steroid/thyroid hormone receptor superfamily of proteins [45–50].

The simplified core of a MAPK cascade consists of three protein kinases: A MAP kinase kinase kinase (MAPKKK), a MAP kinase kinase (MAPKK), and MAP kinase (MAPK); these kinases phosphorylate each other in sequence. When activated, MAPKKK phosphorylates the MAPKK at one or two phosphorylation sites, bringing activation of the MAPKK module. MAPKKs are dual-species kinases: A MAP kinase kinase kinase (MAPKKK), a MAP kinase kinase (MAPKK), and MAP kinase (MAPK); these kinases phosphorylate the MAPKK at one or two phosphorylation sites (almost always a threonine and a tyrosine residue), bringing about activation of the MAPK [45,47]. The active MAPK can then phosphorylate a variety of target proteins throughout the cytoplasm and nucleus. On the internal regulatory mechanisms, each of the kinases in the MAPK cascade is opposed by one or more phospho–protein phosphatases. Thus, for an active MAPKKK to activate a MAPKK, for example, the rate of MAPKK phosphorylation must exceed the rate of MAPK de-phosphorylation. The activities of these phosphatases are high enough to make the output of a MAPK cascade depend upon the continual presence of a stimulus feeding into the cascade; if this particular stimulus is withdrawn, for instance, the downstream kinases become inactivated within a very short lapse of time [48–50].

The best-characterized vertebrate MAPKs fall into three subgroups. The first subgroup includes the founding members of the MAPK family, extracellular signal-regulated kinase-1 (ERK1 or MAPK[ERK1/p44]) and ERK2 (or MAPK[ERK2/p42]), and their closest relatives. This subgroup is often referred to as ERKs, although some ERK proteins are not in fact members of this subgroup family. The second subgroup is the Jun N-terminal kinases (JNKs), so-called because they can activate the Jun transcription factor by phosphorylating two residues near its N-terminus. The third subgroup is the p38 MAPKs, so named because of the molecular weight (38 kDa) of the first representative of the subgroup to be discovered. Members of both the MAPK[ERK] and MAPK[p38] pathways are also classified as stress-activated protein kinases (SAPKs), because they are activated in response to osmotic shock, UV irradiation, inflammatory cytokines and other stressful conditions. In all three subgroups, a large number of M KKks feed into the activation of a smaller number of MAPKKs and MAPKs. The diversity of the MAPKKks thus allows a wide variety of upstream receptors to couple to MAPK cascades [45–50].

On the FMF front, although little is known about the MAPK–FMF interface, the pyrin protein has been recently shown to be regulated in a MAPK[p38]-dependent mechanism in patients with FMF [21]. Of note, thereby, the potential ramifications of the crosstalk between NF-κB and MAPK signaling pathways are of immediate relevance to understanding the molecular pathogenesis of FMF. Therefore, identifying the MAPK signaling pathways associated with evolution of FMF is integral to laying out a preventative approach for treating the molecular evolution of this disease [1,2].

5.3. Cytokines–FMF interface

Levels of blood cytokines and acute phase reactants have been measured in FMF patients and the results provide additional enticing clues [51]. Typical laboratory findings during an attack include leukocytosis, an elevated erythrocyte sedimentation rate and increased acute phase reactants (e.g. serum amyloid A, fibrinogen, C-reactive protein) [52].

Several studies provide evidence that these components are also elevated between attacks in FMF patients [53]. This indicates that though their overt attacks are self-limited in nature, FMF patients operate well above baseline with respect to their inflammatory state. Thus, patients seem poised to react to an otherwise innocuous inflammatory trigger with a vigorous response [54].

5.4. Role for IL-1

Further analysis has revealed that the identification of IL-1 receptor antagonist (IL-1ra) and IL-1β gene polymorphisms may indicate predisposition to FMF but not amyloidosis [55]. Moreover, it was shown that pyrin is capable of regulating IL-1β processing and release in human monocytes and derived macrophages, indicating deregulation in patients with FMF [56]. In contrast, it has been reported that the SPRY domain of pyrin, which is mutated in FMF patients, can interact with inflammasome components and thereby inhibit proIL-1β processing [57].

5.5. Role for IL-2

IL-2 has also been reported involved in the pathogenesis of FMF. For example, IL-2 was elevated among other inflammatory cytokines in the sera of patients with FMF [58] and that the mechanism involved may be associated with the upregulation of soluble interleukin-2 receptor (sIL-2r) [59].

5.6. Role for IL-4

The anti-inflammatory properties of IL-4 are characteristic in FMF. For instance, in vitro stimulation of monocytes with the pro-inflammatory agents interferon (IFN)-γ, TNF, and LPS induced MEFV expression, whereas the anti-inflammatory cytokines IL-4, IL-10, and transforming growth factor (TGF)-β inhibited such expression indicating coordinated expression during FMF inflammatory episodes [60].

Moreover, the mechanism associated with FMF elevation of IFN-γ may be explained by the fact that a defective pyrin is not...
able to inhibit Th1 mediated inflammation [61], a condition pinned ‘impaired Th polarization’ during the inflammatory response characteristic of FMF [62].

5.7. Role for IL-6 and IL-8

A chemotactic cytokine, IL-8 plays a major role in the pathogenesis of FMF. One particular example that exemplifies the aforementioned has been reported with the regulation of leukocyte-endothelial adhesion and leukocyte accumulation in tissues. For instance, it has been shown that increased levels of soluble intercellular adhesion molecule (sICAM)-1 and IL-8 in FMF suggest that neutrophils are active with increased adhesion in FMF [63]. Since increased levels of sICAM-1 are also observed during remission, subclinical disease activity and inflammation seem to be present in some FMF patients.

The role of IL-6 is less prominent than other cytokines in FMF. Contradictory reports have been introducing information about the neutrality of this cytokine. For example, in a comparative study with FMF, it has been shown that IL-6 and IL-8 overproduction was associated with oxidative stress [64–67], indicating that the release of ROS and ROS-related enzymes may comprise a mechanism for the exacerbation of FMF conditions. Furthermore, no eminent role for IL-6 has been reported in G/C polymorphisms associated with FMF with or without amyloidosis [68].

Fig. 4. Molecular mechanisms associated with FMF and MEFV gene, involving the release of proinflammatory cytokines via the activation of apoptosis-dependent caspases, (a) and (b). Pyrin competitively binds with ASC via PYD, preventing its binding to caspase-1 and the formation of the inflammasome, and also binds caspase-1 via B30.2 domain. IL-1β, interleukin 1β; PYD, pyrin domain; NACHT, domain present in neuronal apoptosis inhibitory protein CIITA, HET-E, and TP1; LRR, leucine-rich repeat domain; ASC, apoptosis-associated speck-like protein; CARD, caspase-recruitment domain (adapted, courtesy of Guz et al. [2]).
5.8. Role for IL-10, IL-12, and IL-18

Antagonistic in their effects, hence again IL-10 and IL-12 may represent yet another degree of polarization in FMF. In reinforcement of this situation, it has been reported that both cytokines are elevated at various stages of FMF. For instance, significantly elevated IL-12 levels in FMF patients regardless of activity may suggest the presence of a proinflammatory state also in the inactive period of FMF; however, significant increase in IL-10 levels in FMF group may point to the compensatory suppression of inflammation in active periods of the disease [65]. In contrast, it was shown that the observed decreased IL-10 levels in certain FMF patients may create a tendency to perpetuate subclinical immune activation in the attack-free period [67].

Furthermore, it was reported that IL-12 and IL-18 may contribute to the establishment of Th1 polarization seen in FMF and thus play a part in its pathogenesis [66]. Detection of increased levels of IL-12 and IL-18 in patients with inactive disease may imply that they seem to assist Th1 activation and subclinical inflammation persisting during the attack-free period of the disease, consistent with the abovementioned observation [65].

5.9. Role for TNF

The involvement of TNF and its receptors in FMF are well documented. For instance, it has been shown that a mono-allelic double mutation in TNFRSF1A may be a cause for TNF receptor-associated periodic fever syndrome characteristic of FMF [69].

This is corroborated by the observation that altered extracellular conformation of TNFRI, resulting from the T 50 M mutation in TNFRSF1A, may result in failure of PBMcs to induce an apoptotic response [70]. It is hypothesized that failure to shed TNF/TNFR from the cell surface in patients with the T 50 M mutation (TRAPS) could trigger c-Rel NF-κB activation, and that this would lead to a marked increase in cytokine secretion and an increased proinflammatory response [71]. This mechanism is likely to involve an IL-1-dependent pathway [72].

The schematic shown in Fig. 4 illustrates the cellular and molecular immunologic mechanisms associated with FMF.

6. Conclusions and prospects

A promising avenue is further undertaken by deciphering the underlying cellular and molecular mechanisms associated with the etiology and prognosis of FMF – would the transcriptional scenarios governed by NF-κB/MAPK signaling pathways and the unprecedented role of pleiotropic cytokines represent just been defined immunologic sensors for understanding the realms of the patho-immunobiology of FMF? What remains to be elucidated is the thread-like connection that brings together immunology and systems biology of networks, an association that may well undo the pave way for uncovering therapeutic strategies for alleviating inflammatory-related diseases.

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